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Review Article

Is it Time to Change the Way we Detect Alzheimer's Disease and Monitor its Progression? Towards Affordable and Theory-Driven Approaches from Cognitive Neurosciences

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Abstract

A large proportion of people suffering from Alzheimer's disease (AD) worldwide are not receiving a timely diagnosis. The tools currently used to detect AD and monitor its progression are not sensitive to the preclinical stages and lack specificity for correct diagnosis. Available biomarkers show acceptable levels of sensitivity but remain little specific and not accessible to everyone. We embrace the view that enhancing cognitive assessment of AD should be a research priority. This Perspective paper focuses on issues which, to our view, have been preventing cognitive tests from meeting outstanding needs in the early of detection, monitoring, and treatment development of AD dementia. We first outline the limitations of current diagnostic procedures both theoretically and practically. We then provide a rationale for theory-driven cognitive approaches which would allow mapping assessment tools to specific neuropathological stages of the neurodegenerative course of AD. Finally, we propose research strategies that would help test a hypothesis which, though launched five years ago, remains untested. That is: "Which memory system is impaired first in Alzheimer's disease?"

ABBREVIATIONS

AD: Alzheimer's Disease; CT: Computed Tomography; DLB: Dementia with Lewy Bodies; EEG: Electroencephalogram; ERP: Event-Related Potentials; Fmri: Functional Magnetic Resonance Imaging; FTD: Frontotemporal Dementia; ICOM: International Conference of Memory; MCI: Mild Cognitive Impairment; MRI: Magnetic Resonance Imaging; PD: Parkinson's Disease; PET: Positron Emission Tomography; SCD: Subjective Cognitive Deficits; Vasd: Vascular Dementia; VBM: Voxel-Based Morphometry; VSTMB: Visual Short-Term Memory Binding

INTRODUCTION

Of the 46.8 million people suffering from dementia worldwide, only 20-50% are recognized and documented in primary care. This gap is certainly much greater in low and middle income

countries, with some countries reporting that 90% of sufferers remain unidentified. There is consensus that a large proportion of people suffering from dementia worldwide are not receiving a timely diagnosis, and thus have no access to treatment options or care. What factors drive the under diagnosis of dementia? What could researchers from cognitive neurosciences provide to tackle this global challenge? This paper first focuses on some bottlenecks of current diagnostic procedures and then discusses some approaches which may help improve the detection of AD and monitor its progression.

The pit falls of current diagnostic tools for AD

As awareness about the initial symptoms of AD has grown dramatically over the last few years, people are approaching health services earlier. This is enabling the detection of cognitive impairments from the very early stages which could still be

subjective (i.e., Subjective Cognitive Deficits - SCD [1]) or shortly after entering the objective stages (i.e., Mild Cognitive Impairment - MCI [2]). Although encouraging relative to past diagnostic achievements, recent evidence suggests that these may already be quite late stages in the disease process [1,3,4]. Furthermore, receiving a diagnosis of MCI is providing more problematic than helpful at present as [1], it does not grant certainty about risk of future dementia, [2] does not lead to specific therapeutic strategies, and [3], creates tension and discrepancies within the clinical and scientific community regarding diagnostic approaches, research targets, and therapeutic pathways. To alleviate this tension and overcome some of these barriers a new generation of biomarkers for AD has been developed. Nevertheless, they too experience several limitations [5], which we address in the next section.

Limitations of current biomarkers of AD: AD is associated with severe brain atrophy which can be detected using structural imaging techniques (CT, MRI) (e.g. see [6]). Whilst shrinkage of some brain regions, such as the hippocampus, are thought to be an early signature of AD, standardized values for brain volumes associated with AD that can be measured at a single time point do not exist. Functional imaging techniques (PET, fMRI) often detect reduced brain cell activity (oxygen, glucose uptake is reduced) in patients with AD [7,8]. Nevertheless, neither regional atrophy nor reductions in glucose metabolism are specific to AD [9]. Molecular imaging technologies, using radiotracers targeting the deposit of beta-amyloid and astrocytosis have shown promising results [10,11]. So have tau and beta-amyloid quantification in cerebrospinal fluid [9]. Amyloid plaques in the brain are a characteristic of AD but also of people with no evidence of cognitive decline, making these biomarkers unreliable for diagnostic purposes [12,13]. Moreover, there is an ongoing debate as to whether amyloid or tau pathology is the key driver of AD dementia [14-16]. With the molecular mechanisms of AD pathology still unclear, it remains very challenging to develop effective research strategies towards biomarker development and pharmacological targets.

In addition to these theoretical limitations, biomarkers also hold practical limitations. They are invasive and expensive procedures which are only available in secondary care or specialized centers. Moreover, given the high number of expected patients with AD in the future, the regular use of such techniques as diagnostic tools would be untenable [5]. Biological evidence could be gathered using affordable methodologies such as the EEG (e.g., event related potentials (ERP) and brain connectivity analysis). ERP abnormalities associated with AD have been observed using several paradigms (e.g., Odd-ball: P300, Semantic categorization: N400/P600). Such ERP patterns have also been associated with typical aging, depression and other age-related disorders making them sensitive but not specific to AD (for review see [17]). A recent study indicates that combining cognitive tests which holds maker properties for AD with EEG techniques could help overcome these limitations [18]. The priority is to identify tests of cognitive function which hold such properties. We address this issue next.

Limitations of current cognitive markers of AD: Diagnosis and progression of AD are usually based on performance on

batteries of cognitive tests assessing memory, reasoning, language, attention, etc. While these tests are sensitive to AD, they cannot distinguish AD from other disorders with similar cognitive symptoms (e.g. cognitive aging, depression or other types of dementia) [5]. Most of these tests show improvement on repeated testing, thus masking decline or response to treatment in progressive disorders such as AD [5]. With the advent of preventive initiatives the diagnostic goals have shifted towards the preclinical or subtle symptomatic stages. Most of the tests traditionally used to support the diagnosis of AD and monitor its progression fail at these stages of the disease. To overcome such a limitation composite scores have been introduced [19,20]. Composite scores encapsulate several cognitive abilities which show different sensitivity trajectories to a wide range of neuropsychiatric disorders. Hence, composite scores may boost sensitivity but will dramatically reduce specificity. It is our limited understanding of the links between the pathophysiological mechanisms of the disease and their clinical expression what drives this conundrum. We explore this issue briefly in the following section.

Need for theory-driven markers of AD: Hippocampal-related memory decline is one of the earliest symptoms referred by patients with AD. This long standing view has driven the development of cognitive and neuroimaging markers for AD over the last few decades [3,21]. More specific, regions within the anterior sub-hippocampal areas (i.e. the entorhinal and perirhinal cortex) are affected by AD prior to the hippocampus [22]. MRI-derived volume measures of the entorhinal cortex were better predictors of conversion from MCI to AD than hippocampal volumes were [23,26]. The preclinical phase of AD has been characterized with the presence of neurofibrillary tangles in the trans-entorhinal region [24]. However, to date, it has remained unclear how these different structures of the Medial Temporal Lobe (MTL) contribute to memory. Studies of patients with selective brain damage to these structures show that the anterior sub-hippocampal areas support context-free memory like facts based on familiarly judgements where as context-rich memory such events based on recollection rely on the hippocampus [22]. This made Didic and colleagues hypothesise that impaired context-free, object based, memory might be the first detectable sign in AD [22]. If we consider that such regions are affected by AD earlier than the hippocampus [14,27] and that we now have the possibility to develop tests which can tax their functions, early cognitive markers for AD should therefore focus on the anterior sub-hippocampal regions and their clinical expression [25]. Context-free memory tasks might not be as sensitive to normal aging as cognitive tests currently used for the diagnosis of AD (e.g., associative learning tests; [5,28,29]). Recent studies have started to shed some light on novel memory tasks which seem to meet these and other criteria for a good test for AD.

Good markers to diagnose and monitor AD: Ideally, cognitive markers for AD should (a) be sensitive and specific to AD, (b) not show improvement due to practice effects, (c) not be sensitive to the education or cultural background of the assessed individual, (d) be easy to administer and interpret with minimal training, (e) easily accessible and inexpensive. Importantly, they should be (f) theory driven allowing for the alignment of cognitive constructs and the course of AD pathology [5]. The

selection of such markers should not be predefined but based on clinical stages as defined by the new lexicon [30,31]. That is, some tests can be useful for screening in pre-symptomatic populations while others might help detect degree of impairment, progression, and response to treatment. To date available tests of cognitive function have been indistinctively used to serve all these purposes. This could explain why such tests have lagged behind other molecular markers for AD with regard to their sensitivity [32].

Promising diagnostic tools for the pre-symptomatic stage of AD: Deficits resulting from damage to sub-hippocampal regions may cause symptoms which could be too subtle to be noticed by affected individuals or to cause concern (e.g., lack of familiarity with a face or a place previously experienced, ability to discriminate between two objects' identity). These low level functions provide the building blocks of memory. Memory tests for AD have traditionally assessed higher level memory functions such as those responsible for integrating low level information (e.g., object-based) into complex representations (i.e., episodic memories). Deficits of such functions are noticeable and not only cause concern but also interfere with everyday life tasks. We have now learned more about the link between low level memory functions and their neural correlates within the MTL. What we need to improve is our understanding of the links between AD pathology and such subtle memory impairments. Cognitive markers taxing the low-level memory functions of the sub-hippocampal regions may offer sensitive diagnostic tools for the detection of AD before manifest clinical symptoms occur. Performance on context-free tasks such as recognition of words have shown to be impaired in patients in the pre-symptomatic stages of AD [33]. Sub-hippocampal regions such as the perirhinal cortex also seem to support temporary binding of intra-item associations such as combinations of colour and shapes [34]. These types of visual memory binding deficits (i.e. impairments to temporary bind colour and shape together) have been observed in prodromal stages of sporadic and familial AD [18,35].

Testing Didic et al.'s hypothesis: The recently developed visual short-term memory binding (VSTMB) task has proved informative throughout the continuum of AD [31,35,36]. The VSTMB test can distinguish between healthy aged individuals and AD patients [37], AD patients and those with major depression [38], and between AD and non-AD dementias (i.e., FTD, PD, VasD, DLB) [39]. Furthermore, it can detect impairments in asymptomatic carriers of the E280A presenilin-1 gene mutation [35,40], more than 10 years prior to the onset of dementia. Of note, VSTMB impairments in asymptomatic mutation carriers were observed in the absence of evidence of hippocampal dysfunction [35,40]. VSTMB can be carried out with a damaged hippocampus [41,42], appears affected in the preclinical stages of AD when tests of hippocampal functions are performed perfectly well [35,40], and does not elicit activation of the hippocampus when performed by healthy younger subjects [43]. Hence the VSTMB test is an example of the tasks that can inform about the sub-hippocampal stages of AD [22]. Parra et al., [43] observed that there is a posterior network that involves parietal and occipito-temporal regions supporting VSTMB. The absence of MTL involvement during VSTMB could be largely due

to methodological limitations of fMRI. We need to better map the intrinsic structure of the MTL to ascertain such involvement or lack thereof. Recently, Parra et al., (paper presented in ICOM 2016) used Voxel Based Morphometry (VBM) analysis to investigate the neural correlates of memory binding deficits (relational and conjunctive) in patients with MCI. They found that associative memory functions in the verbal domain relied on an extended network which involves the hippocampus and insular gyrus. Atrophy of these regions accounted for discrepancies in performance between patients and controls. In contrast, poor performance of MCI patients on the VSTMB task (a task assessing memory functions in the visual domain) were only accounted for by atrophy of visual association areas found to be relevant in a previous fMRI study [43]. Although no direct involvement of MTL regions have yet been found during VSTMB, the involvement of areas along the ventral visual stream which are known to feed extra-hippocampal regions such as the entorhinal and perirhinal cortex [44], has been confirmed by two studies. The network supporting VSTMB is more focal than that needed to form associative representations [45]. This could explain why test of associative memory functions are sensitive but not specific to AD as they may be failed by patients suffering from a wider range of brain diseases.

Promising monitoring tools during the symptomatic stages of AD (phase from MCI to AD conversion): Based on Didic et al.[22], the sub-hippocampal stage progresses towards the hippocampal stages of AD. This stage is characterized by impaired context-free and context-rich (episodic) memory and seems to correspond to stage III or IV of the Braak's scale [14]. At this stage patients show autobiographical and topographical memory loss which cause concern and therefore prompt them to seek help advice. The diagnosis of MCI commonly follows. Hence, MCI is the earliest stage of AD that available tests of episodic memory can identify [46,47]. Hippocampal-derived impairments are responsible for cognitive decline which alters everyday life functioning (e.g., being unable to remember where you left the car keys or where the car was parked) [48]. Context-rich tasks could therefore provide valuable information about effectiveness of medication or treatments during the symptomatic stage of AD. For a recent review of promising context rich tasks see Rentz and colleagues [31]. Besides these promising novel tasks, assessment of other cognitive functions (e.g. memory, reasoning, executive function - for overview see Logie and colleagues [5]) remains useful to monitor cognitive decline in individuals diagnosed with MCI as well as to interpret functional decline.

From theory-driven assessment to theory-driven interventions: With the advent of prevention initiative for AD, cognitive makers which meet the needs discussed above are of upmost priority. However, to date, no effective pharmacological treatments for patients with MCI or dementia have been identified. Previous pharmacological trials have only shown sub threshold effects on behavior, cognition and function [49]. The extent to which these null findings are the result of ineffective drugs, poor outcome measures (e.g., cognitive scores), or inconsistency in rating procedures is not fully understood. There is a general consensus that improvement of cognitive scoring and rating procedures are required. Good tests of cognitive function cannot only inform pharmacological treatments but also provide theory

to develop non-pharmacological interventions. Some studies have shown that cognitive interventions can have a positive effect on patients with MCI [50-53]. A new line of investigation is focusing on the development virtual reality (VR) applications [54-56]. The high ecological validity of VR technologies make VR a promising tool for both neuropsychological assessment and intervention [57-61]. Several studies have ascertained the efficiency of VR supporting both patients in the early stages of dementia and their family by giving educational support and memory assistance [62-65]. To date, several research studies have addressed specific aspects of cognitive impairments in AD using VR. A good summary of the relevant studies have been described in the mini-review by García-Betances et al. [55]. The authors reported VR benefits for every cognitive function investigated (e.g. attention, memory, and executive functions). At the same time, VR seems to be a valid tool for memory training in subjects with MCI [65-67].

CONCLUSIONS

This critical appraisal of the context wherein AD research currently delves into a prioritized set of needs leads us to present some recommendations which may be considered by future research strategies.

1. A new research pathway to map effective tests of cognitive function to progression of neuropathology in AD following the new lexicon.
2. Refining knowledge about the fine-grained functional and anatomical structure of the MTL and its vulnerability to AD-related amyloid and tau pathology.
3. Identifying suitable theory-driven memory tests to screen for, support the diagnosis, and monitor the progression of AD dementia.
4. Development of theory-driven cognitive interventions to aid the frail elderly and support those transiting through the continuum of AD.

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